Diesel engine exhaust (CASRN N.A.)

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Note: Support Documents are available for the Diesel engine exhaust assessment in Adobe PDF Format. Similar documents can be found in the List of Available IRIS Toxicological Reviews and Other Support Documents.

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Diesel engine exhaust; CASRN N.A.

Health assessment information on a chemical substance is included in IRIS only after a comprehensive review of chronic toxicity data by U.S. EPA health scientists from several Program Offices, Regional Offices, and the Office of Research and Development. The summaries presented in Sections I and II represent a consensus reached in the review process. Background information and explanations of the methods used to derive the values given in IRIS are provided in the Background Documents.

STATUS OF DATA FOR Diesel engine exhaust

File First On-Line 06/01/1993

Category (section)	Status	Last Revised
Oral RfD Assessment (I.A.)	no data	02/28/2003
Inhalation RfC Assessment (I.B.)	on-line	02/28/2003
Carcinogenicity Assessment (II.)	on-line	02/28/2003

_I. Chronic Health Hazard Assessments for Noncarcinogenic Effects

_I.A. Reference Dose for Chronic Oral Exposure (RfD)

Substance Name — Diesel engine exhaust
CASRN — N.A.
Last Revised — 02/28/2003

The oral Reference Dose (RfD) is based on the assumption that thresholds exist for certain toxic effects such as hemolysis. It is expressed in units of mg/kg-day. In general, the RfD is an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. Please refer to the Background Document for an elaboration of these concepts. RfDs can also be derived for the noncarcinogenic health effects of substances that are also carcinogens. Therefore, it is essential to refer to other sources of information concerning the carcinogenicity of this substance. If the U.S. EPA has evaluated this substance for potential human carcinogenicity, a summary of that evaluation will be contained in Section II of this file.

An oral RfD for diesel engine exhaust is not provided. All available studies are focused on inhalation exposure.

_I.B. Reference Concentration for Chronic Inhalation Exposure (RfC)

Substance Name — Diesel engine exhaust
CASRN — N.A.
Last Revised — 02/28/2003

The inhalation Reference Concentration (RfC) is analogous to the oral RfD and is likewise based on the assumption that thresholds exist for certain toxic effects such as cellular necrosis. The inhalation RfC considers toxic effects for both the respiratory system (portal-of-entry) and systems peripheral to the respiratory system. It is generally expressed in units of mg/m³. In general, the RfC is an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily inhalation exposure of the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. Inhalation RfCs were derived according to the Interim Methods for Development of Inhalation Reference Doses (EPA/600/8-88/066F August 1989) and subsequently, according to Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry (EPA/600/8-90/066F October 1994). RfCs can also be derived for the noncarcinogenic health effects of substances that are carcinogens. Therefore, it is essential to refer to other sources of information concerning the carcinogenicity of this substance. If the U.S. EPA has evaluated this substance for potential human carcinogenicity, a summary of that evaluation will be contained in Section II of this file.

Diesel engine exhaust (DE) is a complex mixture of airborne particles and gases. Diesel particulate matter (DPM), composed of elemental carbon particles and adsorbed organic compounds, is the most frequently determined measure of DE and the measure reported in toxicological studies of diesel engine exhaust. The previous RfC of 5×10^{-3} mg DPM/m³ was entered on IRIS 6/1/93. This updated RfC reflects the use of a revised model for lung deposition of DPM, and remains unchanged.

__I.B.1. Inhalation RfC Summary

Critical Effect	Experimental Doses*	UF	MF	RfC
		30	1	5μg/m³
Pulmonary inflammation and histopathology Rat chronic inhalation study Ishinishi et al. (1988)	NOAEL: 0.46 mg/m³ $NOAEL_{HEC}$: 0.144 mg DPM/m³			

*Conversion Factors and Assumptions — Human equivalent concentrations were derived using a mathematical model of diesel particulate matter (DPM) deposition and clearance (Yu et al., 1991), assuming that equal pulmonary surface loadings (in mg DPM/cm²) in rats and humans would be associated with similar effects. First, the model was used to estimate the loading in rats corresponding to the NOAEL, administered 16 hr/day, 6 days/week, for 130 weeks. Then the model was used to estimate the continuous exposure conditions for humans which would lead to the loading estimated in rats. In performing the modeling, rats were taken to weigh 300g, with a total pulmonary surface area of 4090 cm². Human equivalent concentrations were derived using respiratory parameters for a 25 year-old human male having a total pulmonary surface area of 627,000 cm², tidal volume of 0.926 L, respiratory frequency of 15 breaths/min, and total daily pulmonary volume of 20 m³, with exposure assumed to last 70 years. For more details of the derivation of human equivalent concentrations, see the Support Document (U.S. EPA, 2002; Appendix A).

__I.B.2. Principal and Supporting Studies (Inhalation RfC)

Chronic respiratory effects are the principal noncancer hazard to humans from long-term environmental exposure to diesel engine exhaust, or emissions (DE). Several occupational studies have evaluated the noncancer effects of chronic exposure to DE (U.S. EPA, 2002, Chapter 5.1.1.2). There is some evidence suggesting that exposure may impair pulmonary function, though the results are not robust. While the increased occurrence of mostly transient symptoms such as cough, phlegm, and chronic bronchitis is clear in noncancer occupational studies, the studies are deficient in exposure information.

Other effects (e.g., neurological, growth and survival, neurobehavioral, lowered resistance to respiratory infection, liver effects) are observed in animal studies at higher exposures than those producing the respiratory effects (U.S. EPA, 2002, Chapter 5.6). The human and animal data for the immunological effects of DE exposure (i.e., exacerbation of allergenicity, and asthma symptomology) are currently inadequate for dose-response evaluation. Reproductive toxicity has been evaluated in six studies. No teratogenic, embryotoxic, fetotoxic or female reproductive effects have been observed in mice, rats, or rabbits at inhalation exposure levels lower than those where respiratory effects were observed. Respiratory effects are considered the "critical effect" for the derivation of a chronic RfC for DE.

The evidence for chronic respiratory effects is based mainly on animal studies showing consistent findings of inflammatory, histopathological (including fibrosis), and functional changes in the pulmonary and tracheobronchial regions of laboratory animals, including the rat, mouse, hamster, guinea pig, monkey, and cat. Of 17 studies covering these species, the rat is the most studied test animal, though positive responses are also seen in mice, guinea pigs, monkeys, and hamsters. Most are single dose studies, except for five multi-dose studies discussed below.

The multi-dose studies, by Ishinishi et al. (1986, 1988), Mauderly et al. (1987a), Heinrich et al. (1995), and Nikula et al. (1995), show exposure-response relationships based on chronic

inhalation exposure to whole diesel exhaust in rats. The effects observed include inflammation, histopathology (including fibrosis), and functional changes in the pulmonary and tracheobronchial regions. An array of these key studies and their effect levels (NOAEL, LOAEL, $BMCL_{10}$, AEL) prior to conversion to human equivalent concentrations (HECs) is shown in Table I.B.1. This array provides an inter-study concentration-response continuum, normalized to human equivalent continuous diesel particulate matter (DPM) exposure levels, facilitating the choice of a concentration to use as a point of departure in deriving an RfC.

TABLE I.B.1: Human equivalent continuous concentrations: 70-year HECs calculated with the model of Yu et al. (1991) from key long-term studies of rats repeatedly exposed to DPM[a]

Study	Exposure concentration (mg/m^3)	Effect level[a]	Lung burden (modeled) (µg DPM /cm^2)[b]	HEC (mg/m^3)
Ishinishi et al. (1988) (LD)[c]	0.11	NOAEL	0.0587	0.032
Mauderly et al. (1987a)	0.35	NOAEL	0.0685	0.038
Ishinishi et al. (1988) (LD)[c]	0.41	NOAEL	0.245	0.128
Ishinishi et al. (1988) (HD)[c]	0.46	NOAEL	0.281	0.144
Heinrich et al. (1995)	0.84	LOAEL	0.94	0.33
Nikula et al. (1995)	2.44 & 6.3[d]	$BMCL_{10}$ - inflam	1.34	0.37
Ishinishi et al. (1988) (HD)[c]	0.96	LOAEL	3.16	0.883
Ishinishi et al. (1988) (LD)[c]	1.18	LOAEL	4.50	1.25
Nikula et al. (1995)	2.44 & 6.3[d]	$BMCL_{10}$ - fibrosis	4.70	1.3
Mauderly et al. (1987a)	3.47	LOAEL	4.95	1.375
Nikula et al. (1995)	2.44	LOAEL	7.00	1.95
Ishinishi et al. (1988) (HD)[c]	1.84	AEL	7.63	2.15
Heinrich et al. (1995)	2.5	AEL	8.40	2.35
Ishinishi et al. (1988) (LD)[c]	2.32	AEL	9.75	2.75
Mauderly et al. (1987a)	7.08	AEL	10.9	3.05

Ishinishi et al. (1988) (HD)[c]	3.72	AEL	15.8	4.4

[a] Effect levels are based on the critical effects of pulmonary histopathology and inflammation as reported in the individual studies. NOAEL: no-observed-adverse-effect level; LOAEL: lowest-observed-adverse-effect level; AEL: adverse-effect level; $BMCL_{10}$: lower 95% confidence estimate of the concentration of diesel particulate matter (DPM) associated with a 10% incidence of chronic pulmonary inflammation (inflam) or fibrosis (see Appendices A and B for more specifics).

[b] Lung burdens were derived from data generated from the animal portion of the Yu model using the concentration and duration scenario of each study. The human portion of the Yu model was then used to estimate the continuous, 70-year exposures that would result in this same lung burden, i.e., the HEC. See Table A-4 in Appendix A and accompanying text for further specifics on derivation.

[c] LD/HD = light-duty/heavy-duty diesel engine.

[d] These values are the actual exposure levels used in the Nikula study. These values were converted into HEC and entered into bench mark concentration (BMC) equations to obtain the estimate of the $BMCL_{10}$ listed. The lung burdens for the two $BMCL_{10}$s listed here were derived by interpolation.

Among these five studies, the study with the highest NOAEL is Ishinishi et al. (1988). In this study, Fischer 344 rats (120 males and 95 females/exposure level) were exposed for 16 hours/day, 6 days/week for 30 months to 0.11, 0.41, 1.18, or 2.32 mg/m³ DPM from a light-duty (LD) engine, or to 0.46, 0.96, 1.84, or 3.72 mg/m³ DPM from a heavy-duty (HD) engine. Equivalent duration-adjusted concentrations were 0.063, 0.23, 0.67, or 1.3 mg/m³ DPM from LD engine exhaust and 0.26, 0.55, 1.05, or 2.13 mg/m³ DPM from HD engine exhaust. Hematology, clinical chemistry, urinalysis, and light and electron microscopic examinations of histopathology were performed. Findings included minor body weight changes and equivocal alterations in liver and kidney function. The body weight of female rats exposed to 3.72 mg/m³ was 15-20% less than controls throughout the study. A dose-dependent decrease in body weight of the other groups was mentioned, but neither data nor statistical analyses are reported. In addition, although impaired liver and kidney function were indicated by changes in serum measures (increased liver enzyme activities and increased urea nitrogen, electrolyte levels, gamma globulin concentration and reduced total blood proteins), neither was confirmed histopathologically.

More notably, while no histopathological changes were observed in the lungs of rats exposed to 0.46 mg/m³ DPM or less, at higher concentrations, severe morphological changes were observed, including shortened and absent cilia in the tracheal and bronchial epithelium, marked hyperplasia of the bronchiolar epithelium, and swelling of the Type II cellular epithelium. There was no difference in the degree of changes in pulmonary pathology at similar exposure concentrations between the LD and the HD series, however. This study identifies LOAELs for chronically exposed rats at 1.18 and 0.96 mg/m³ (actual exposure) for LD and HD series and NOAELs at 0.41 and 0.46 mg/m³ (actual) for LD and HD engines.

Human equivalent concentrations corresponding to the animal NOAEL, LOAEL, AEL, and $BMCL_{10}$ values were computed using a dosimetry model developed by Yu et al. (1991), as described in the Support Document (U.S. EPA, 2002; Chapter 6.5.2, and Appendix A). The dosimetry model accounts for species differences (rat to human) in respiratory exchange rates, particle deposition efficiency, differences in particle clearance rates at high and low doses, and transport of particles to lymph nodes. Because the particle sizes are not reported for the NOAEL for the 0.41 mg/m³ LD group or the 0.46 mg/m³ HD group, the size distributions for these are assumed to be the same as the next highest group. Thus, for both LD and HD series, the LOAEL(HEC) and NOAEL(HEC) are estimated using the particle

deposition and retention model developed by Yu and Yoon (1990) using the same MMAD and sigma g. The resulting LOAEL(HEC) for the LD and HD series are 1.25 and 0.883 mg/m³, respectively. The NOAEL(HEC) for the LD and HD series based on the retention model are 0.128 and 0.144 mg/m³, respectively.

The single-dose studies provide valuable supporting information for designation of the critical effect of pulmonary histopathology. These studies [Heinrich et al. (1982, 1986), in hamsters, mice, and rats; Iwai et al. (1986) in rats; Lewis et al. (1989) in monkeys; and Pepelko (1982a) in rats] are all single-dose analyses conducted to study mechanisms or the comparative responses of different species. For instance, the single-dose monkey study (Lewis et al., 1989) at 1.95 mg/m³ showed minor precursor symptoms consistent with airway and lung toxicity, but no fibrosis, inflammation or emphysema; the duration of exposure was also relatively short. The lack of any clear dose-response data, however, precludes consideration of these studies as a quantitative basis for RfC derivation. Likewise, studies of chronic, multiple-level exposure involving species other than rats, i.e., hamsters (Pepelko, 1982b), cats (Plopper et al., 1983), and guinea pigs (Barnhart et al., 1981, 1982), provide cross-species corroboration of the critical effects of pulmonary histopathology and inflammatory alteration.

__I.B.3. Uncertainty and Modifying Factors (Inhalation RfC)

The highest human equivalent dose associated with no apparent effect ($NOAEL_{HEC}$) is 144 µg DPM/m³ from the Ishinishi et al. (1988) study; this becomes the point of departure for deriving an RfC. To obtain the RfC, this point of departure was divided by two types of uncertainty factors (UFs): a factor of 3 recognizes residual interspecies (i.e., rat to human) extrapolation uncertainties, and a factor of 10 reflects uncertainties about interindividual human variation in sensitivity.

Kinetic differences between rats and humans were addressed through the use of a dosimetry model. Although there is uncertainty in the dosimetry model, as in the application of most kinetic models, U.S. EPA guidance (U.S. EPA, 1994) recommends no further quantitative adjustment for uncertainty in the modeling results without chemical-specific data. In this case, the maximum default interspecies extrapolation UF is reduced from 10 to 3, due to the use of the dosimetry model to account for kinetic differences. The use of 3, the full amount of this UF addressing only interspecies differences in pharmacodynamics, is supported by several studies suggesting that humans may be as sensitive or somewhat more so than rats for respiratory tract inflammation.

In the absence of mechanistic or specific data, a default value of 10 is considered appropriate to account for possible human variability in sensitivity, particularly for children and people with preexisting respiratory conditions. The spectrum of the population that may have a greater susceptibility cannot be better characterized until there is additional knowledge about mode of action.

The point of departure was derived from a chronic study, therefore an UF for using a study of less than chronic duration of exposure is unnecessary. In addition, evaluation of chronic effects other than respiratory effects, as well as some aspects of reproductive and developmental toxicity, showed that none of these effects were expected to occur at DPM levels lower than the identified point of departure. While data demonstrating immunological and allergenic effects were suggestive, the available database specific to diesel engine exhaust does not support further adjustment of the RfC. Consequently, an UF for database adequacy was not judged necessary.

__I.B.4. Additional Studies/Comments (Inhalation RfC)

There is no specific information in humans showing that children are more susceptible to DE's chronic respiratory effects. Limited data from studying children exposed to "black smoke" (presumed to be a surrogate for DPM), through attending schools near freeways, indicates that childrens' reactions (respiratory symptomology and reduced lung function) are no different than adult reactions (van Vliet et al., 1997; Brunekreef et al., 1997, 2000). One study in rats (Mauderly, 1987b) showed that DE did not affect the developing rat lung more severely than the adult rat lung, and in fact that particle clearance was faster in the younger lung.

While diesel exhaust is a mixture of gases and particles, health concerns have long focused on DPM, and the organics adhering to the particles. DPM is considered to be the prime etiologic agent of noncancer health effects when DE is sufficiently diluted to limit the concentrations of gaseous irritants (NO_2 and SO_2), irritant vapors (aldehydes), CO, or other systemic toxicants (U.S. EPA, 2002). The small size of DPM, combined with large surface area, likely enhances the potential for subcellular interactions with important cellular components of respiratory tissues, once the particles are inhaled by humans or other species (Johnston et al., 2000; Oberdörster et al., 2000). Mode-of-action information about respiratory effects from DE exposure indicates that, at least in rats, the pathogenic sequence

characterized in four animal species, are considered relevant to humans, though animal data are still being used to predict a human hazard. Although in general the rat is thought to be more sensitive to lung injury than humans to poorly soluble particles (ILSI, 2000), it is not clear that this is the case specifically for diesel exhaust particulates and the resulting inflammation effects. Since DE is a mixture of not just carbon particles but also various organics, both on the particles and in gases, there is some concern that the full impact of DE has not been assessed. In addition, differences in particle deposition, retention, and clearance mechanisms have been largely but perhaps not completely addressed by the use of the rat-to-human dosimetry model. In terms of the potential for other critical health effects, there is growing evidence suggesting that DE can exacerbate allergenic effects to known sensitizers, while also evoking production of biochemical markers typically associated with asthma. While some work in this area indicates that humans may be as sensitive as rats and mice to the immunologic effects (U.S. EPA, 2002; Chapter 6.3.4), this database is currently lacking key exposure-response data. It also should be noted that the ambient PM health effects data show a broader array of adverse human health concerns (e.g., cardiovascular effects, as well as acute exposure effects).

__I.B.6. EPA Documentation and Review of the Inhalation RfC

Source Document — U.S. EPA, 2002

The Health Assessment Document (HAD) on which this IRIS Summary is based was peer reviewed by EPA's Clean Air Science Advisory Committee (CASAC) in October 2000. Written comments from CASAC were received in December 2000. Their comments were evaluated carefully and incorporated in finalization of the HAD. A record of these comments is available with the HAD.

Agency Consensus Date - 1/31/03

__I.B.7. EPA Contacts (Inhalation RfC)

Please contact the IRIS Hotline for all questions concerning this assessment or IRIS, in general, at (202)566-1676 (phone), (202)566-1749 (fax), or hotline.iris@epa.gov (E-mail address).

_II. Carcinogenicity Assessment for Lifetime Exposure

Substance Name — Diesel engine exhaust
CASRN — N.A.
Last Revised — 02/28/2003

Section II provides information on three aspects of the carcinogenic assessment for the substance in question, the weight-of-evidence judgment of the likelihood that the substance is a human carcinogen, and quantitative estimates of risk from oral exposure and from inhalation exposure. The quantitative risk estimates are presented in three ways. The slope factor is the result of application of a low-dose extrapolation procedure and is presented as the risk per (mg/kg)/day. The unit risk is the quantitative estimate in terms of either risk per µg/L drinking water or risk per µg/m³ air breathed. The third form in which risk is presented is a concentration of the chemical in drinking water or air associated with cancer risks of 1 in 10,000, 1 in 100,000, or 1 in 1,000,000. Users are referred to Section I of this IRIS file for information on long-term toxic effects other than carcinogenicity.

_II.A. Evidence for Human Carcinogenicity

__II.A.1. Weight-of-Evidence Characterization

Using U.S. EPA's revised draft 1999 Guidelines for Carcinogen Risk Assessment (U.S. EPA, 1999), diesel exhaust (DE) *is likely to be carcinogenic to humans* by inhalation from environmental exposures. The basis for this conclusion includes the following lines of evidence:

- strong but less than sufficient evidence for a causal association between DE exposure and increased lung cancer risk among workers in varied occupations where exposure to DE occurs;
- extensive supporting data including the demonstrated mutagenic and/or chromosomal effects of DE and its organic constituents, and knowledge of the known mutagenic and/or carcinogenic activity of a number of individual organic compounds that adhere to the particles and are present in the DE gases;
- evidence of carcinogenicity of DPM and the associated organic compounds in rats and mice by other routes of exposure (dermal, intratracheal, and subcutaneous and intraperitoneal injection); and
- suggestive evidence for the bioavailability of DE organic compounds from DE in humans and animals.

It is noted that there are also several well conducted studies in rats that show that inhalation exposure to diesel exhaust results in lung tumors, while results in other traditional rodent test species are equivocal or not positive for inhalation induced lung tumors. There is a substantial body of evidence showing that the rat is more responsive than other species to the induction of lung tumors by poorly soluble particles, with diesel exhaust particles being one example. While directly comparable human data are lacking, some human cohorts exposed to very high levels of poorly soluble particles (e.g., coal miners) do not show the sequence of events leading to lung tumors that has been seen in rats. This mode-of-action information for the rat, involving particle overload and consequent persistent inflammation and cell proliferation, supports a nonlinear mode of action for lung cancer in the rat (ILSI, 2000). The nonlinear cancer response is further characterized as occurring at relatively high exposures of diesel exhaust (>3500 µg DPM/m^3 DPM), which is far beyond the range of environmental levels. The rat tumor occurrences, thus, are not particularly influential in judging the hazards at environmental levels of exposure.

Support for a human cancer hazard at environmental levels of exposure comes from two considerations: (1) the evidence for a mutagenic mode of action, and (2) exposure comparisons. Concern for a human cancer hazard is consistent with EPA's science policy position that assumes a linear response for carcinogens with a mutagenic component, in the absence of definitive data demonstrating a nonlinear mechanism. Additional support for an environmental hazard also comes from a comparison of the estimated environmental levels to the estimated occupational exposure levels where risk is observed in many studies. Given that there is only a minimal margin between environmental and occupational exposure ranges, if not an overlap, the extrapolation of observable hazard from the occupational setting to the ambient environment is relatively confident.

Overall, the qualitative evidence for potential human carcinogenicity for DE is considered strong, even though inferences are involved and uncertainties are present. First, there has been a considerable scientific debate about the significance of the available human evidence for a causal association between occupational exposure and increased lung cancer risk. Some experts view the evidence as weak and/or inconsistent while others consider the evidence compelling, due to a lack of consensus about whether the effects of smoking and other

potential confounders have been adequately accounted for in key studies, and the lack of agreed-upon historical DE exposure data for the key studies. These issues highlight the difficulty in delineating an exposure-based dose-response relationship. In addition, while the mode of action for lung tumors in rats at high DE exposures is sufficiently understood, the mode of action for the DE lung cancer risk in humans is not known. To date, available evidence for the role of both the adsorbed organics and the carbon core particle has only been shown under high-exposure experimental animal test conditions. There is virtually no information about the relative role of DE constituents in mediating carcinogenic effects at the low-exposure levels or in humans.

Data gaps also limit conclusions regarding the full extent of DE's carcinogenic potential. These limitations include lack of knowledge concerning the susceptibility of young animals to DE's carcinogenic effects relative to more mature animals, the human carcinogenic potential of DE by oral and dermal exposures, and the inconclusive epidemiologic evidence for DE being associated with other forms of cancer.

__II.A.2. Human Carcinogenicity Data

A persistent association of risk for lung cancer associated with DE exposure has been observed in more than 30 epidemiologic studies published in the literature over the past 40 years. The majority of the epidemiologic studies evaluate distinct populations of occupational groups, including railroad workers, truck drivers, heavy-equipment operators, farm tractor operators, and professional diesel vehicle drivers. The remaining studies include reanalyses of specific studies, and three meta-analyses. The Support Document (U.S. EPA, 2002; Section 7.2) provides a review of this literature.

Increased lung cancer risk has been observed in 8 out of 10 cohort studies, 5 of which were statistically significant. Increased lung cancer risk has also been observed in 10 of 12 case-control studies, 8 of which were statistically significant. Overall, the increased lung cancer relative risks generally range from 1.2 to 1.5, although a few studies show overall relative risks as high as 2.6. Statistically significant increases in relative risk (RR), 1.33 to 1.47, are also shown in two independent meta-analyses of epidemiologic studies. The meta-analyses demonstrate the effect of pooling many studies and in this case show the positive relationship between DE exposure and lung cancer across a variety of DE-exposed occupations. The strongest studies are summarized below.

The most extensive study linking lung cancer and diesel engine exhaust is the case-control study by Brüske-Hohlfeld et al. (1999). These investigators conducted a pooled analysis of two case-control studies among male workers occupationally exposed in Germany (Jöckel et al., 1995, 1998; Wichmann et al., 1988). Lung cancer cases and controls matched for sex, age, and region of residence were selected randomly from compulsory municipal registries. The investigators collected data on demographic information, detailed smoking, and occupational history for 3,498 cases and 3,541 controls. Job titles and industries were classified in 33 and 21 categories, respectively. Job descriptions were written and verified to avoid misclassification of estimation of exposure to diesel engine exhaust. Individual cumulative exposures were estimated by categorizing the duration of exposure determined from complete work histories. Smoking information in pack-years was calculated from personal interview information. Asbestos exposures were estimated by certain job-specific supplementary questions.

This study shows increased risk for all DE-exposed job categories. Analyses yielded statistically significant ORs ranging from 1.25 (95% CI = 1.05, 1.47) for professional drivers,

to 2.31 (95% CI = 1.44, 3.7) for heavy equipment operators, adjusted for smoking and asbestos exposure. These investigators presented analyses by various job categories, by total years of exposure, calendar year of first and end exposure and, when possible, separately for West and East Germany. Significantly higher risks were found among all four job categories. For professional drivers (of trucks, buses, and taxis) ORs ranged from 1.25 to 2.53. For other traffic-related jobs (switchmen, diesel locomotive drivers, diesel forklift truck drivers), ORs ranged from 1.53 to 2.88. For heavy equipment operators (bulldozers, graders, and excavators), ORs ranged from 2.31 to 4.3, and for drivers of farming equipment the only significant excess (OR = 6.81, 95% CI = 1.17, 39.5) was for exposure for >30 years.

The professional drivers and the other traffic-related jobs also have some mixed exposures to gasoline exhaust in general traffic. On the other hand, it should be noted that exposure to DE among heavy equipment and farm tractor drivers is much higher and not as mixed as in professional drivers. The heavy equipment drivers usually drive repeatedly through their own equipment's exhaust. Therefore, the observed highest risk for lung cancer in this job category establishes a strong link with the DE. Only one other study found a significantly higher relative risk (RR) for heavy equipment operators, at 2.6 (Boffetta and Stellman, 1988). Although the only significant excess in the group was observed for farming tractor operators with more than 30 years of exposure, a steady increase in risk was observed for this job category with increasing exposure. The investigators stated that the working conditions and the DE of tractors remained fairly constant over the years. This increase may be due mainly to exposure to DE and PM_{10}.

The main strengths of the study are large sample size, resulting in good statistical power; inclusion of incident cases diagnosed not more than 3 months prior to the interview; use of only personal interviews, reducing recall bias; diagnoses ascertained by cytology or histology; and availability of lifelong detailed occupational and smoking history. Exposure estimation done for each individual was based on job codes and industry codes, which were validated by written job descriptions to avoid misclassification. The main limitation of the study is lack of data on actual exposure to DE. The cumulative quantitative exposures were calculated on the basis of time spent in each job with potential exposure to DE and the type of equipment used. Thus, this study provides strong evidence for causal association between exposure to diesel exhaust and occurrence of lung cancer.

In addition to the study by Brüske-Hohlfeld et al. (1999), evidence for a lung cancer hazard comes from several other case-control studies: among railroad workers by Garshick et al. (1987), and among truck drivers of the Teamsters Union by Steenland et al. (1990), among truck drivers, railroad workers. Garshick et al. (1987) found increased risk of lung cancer associated with increasing cumulative exposure to diesel engine exhaust. The investigators used US Railroad Retirement Board records to identify 1,319 lung cancer deaths and 2,385 matched controls. An analysis using number of years in a diesel-exposed job as a continuous variable, and adjustment for asbestos and smoking, yielded an odds ratio (OR) of 1.41 (95% CI = 1.06, 1.88) for ≥20 years of DE exposure in the <64 years of age group. When DE exposure was categorized as 0 to 4, 5 to 19, and ≥20 diesel years, the risk of lung cancer in the same group increased when compared to the 0- to 4-year group, with an OR of 1.64 (95% CI = 1.18, 2.29). This appears to be a well-conducted and well-analyzed study with reasonably good power. Potential confounders were controlled adequately, and interactions between diesel exhaust and other lung cancer risk factors were tested. Some of the limitations of this study are inadequate latency period, misclassification of exposure because Interstate Commerce Commission job classifications were used as a surrogate for exposure, and use of death certificates for identification of cases and controls.

Steenland et al. (1990) also observed an increased risk of lung cancer with increasing years of exposure. The investigators studied lung cancer deaths in Teamsters Union truck drivers and support personnel, using death certificates from pension files to identify 1,058 cases and 1,160 controls. Information on work history and potential confounders were collected from next-of-kin interviews. Using duration of employment as a categorical variable and considering employment after 1959 (when presumed dieselization occurred for most trucking companies), the risk of lung cancer increased with increasing years of exposure, for both long-haul and short-haul drivers. Using 1964 as the cutoff, a similar trend was observed for long-haul drivers. Using 1964 as the cutoff (presumed dieselization for independent driver and non-trucking firms), long-haul drivers continued to show a significant positive trend, while short-haul drivers did not show a positive trend. For truck drivers who primarily drove diesel trucks and worked for 35 years, the OR was 1.89 (95% CI = 0.81, 2.22). The main strengths of the study are availability of detailed records from the Teamsters Union, a relatively large sample size, availability of smoking data, and measurements of exposure. The limitations of this study include possible misclassifications of exposure and smoking, lack of levels of diesel exposure, a smaller nonexposed group, and an insufficient latency period.

Substantive evidence from cohort studies linking diesel exhaust exposure to lung cancer comes from the Garshick et al. (1988) study of 55,407 railroad workers, conducted in the United States. Relative risks (RRs) of 1.57 (95% CI = 1.19, 2.06) and 1.34 (95% CI = 1.02, 1.76) were found for ages 40 to 44 and 45 to 49, respectively, after the exclusion of workers exposed to asbestos. The investigators reported that the risk of lung cancer increased with increasing duration of employment. As this was a large cohort study with a lengthy follow-up and adequate analysis, including dose response (based on duration of employment as a surrogate) as well as adjustment for other confounding factors such as asbestos, the observed association between increased lung cancer and exposure to diesel exhaust is more meaningful.

Reanalyses of the Garshick et al. (1988) study yielded varying conclusions. Crump et al. (1991) found that the relative risk could be positively or negatively related to duration of exposure depending on how age was controlled. Additional analysis by Garshick et al. (1991) found that the relationship between years exposed, when adjusted for the attained age, and calendar years was flat to negative, depending on the choice of the model. They also found that deaths were under-reported by approximately 20% to 70% between 1977 and 1980, and their analysis based on job titles, limited to 1959-1976, showed that the youngest workers still had the highest risk of dying of lung cancer. An analysis of the same data by California EPA (Cal EPA, 1998) yielded a positive dose response, using age at 1959 and an interaction term of age and calendar year in the model. Crump (1999) reported that the negative dose-response continued to be upheld in his latest analysis when age was controlled more carefully and years of exposure quantified more accurately. Crump (1999) also asserted that the negative dose response trends for lung cancer observed either with the cumulative exposure or duration of exposure may be due to the under-ascertainment of deaths in last 4 years of follow-up of the Garshick et al. (1988) study, as well as to incomplete follow-up in earlier years.

A HEI special panel (HEI, 1999) conducted their own analyses of the Garshick et al. (1988) data to support quantitative risk assessment, and found similar results as Crump et al. (1991) and Garshick (1991). The HEI panel reported consistently elevated risk of lung cancer for train workers compared to clerks for each duration of employment, and an intermediate risk of lung cancer for shop workers; however, they found decreasing risk of lung cancer with increasing duration of employment. The panel discussed various possibilities for the negative dose response and advised against using the Garshick et al. (1988) data for quantitative risk

assessment. These possible explanations included biases such as unmeasured confounding by smoking, exposure to other sources of pollution, previous occupations exposures, exposure misclassification, use of "duration of employment" as a surrogate measure for exposure, health worker survivor effect, and differential or incomplete ascertainment of lung cancer deaths. The panel also reported the strengths of Garshick et al. (1988) study, such as large population, control for asbestos and smoking, and concluded that the study was generally consistent with findings of weak association between exposure to diesel exhaust and occurrence of lung cancer. The divergent results of these recent analyses do not negate the positive evidence this study provides for the weight-of-evidence evaluation.

Three aggregate analyses of studies concerned with the relationship of diesel exhaust exposure and lung cancer risk are Cohen and Higgins (1995), Bhatia et al. (1998), and Lipsett and Campleman (1999). The Cohen and Higgins (1995) report is a qualitative review of 35 epidemiologic studies (16 cohort and 19 case-control) of occupational exposure to diesel engine exhaust published between 1957 and 1993. Control for smoking was identified in 15 studies. Six of the studies (17%) reported RR estimates less than 1, whereas 29 (83%) reported at least one RR greater than one, indicating a positive association. Twelve studies indicating a RR greater than 1 had 95% confidence intervals that excluded unity. The evidence suggests that occupational exposure to diesel exhaust from diverse sources increases the rate of lung cancer by 20% to 40% in exposed workers generally, and to a greater extent among workers with prolonged exposure. They also found that the results are not explicable by confounding due to cigarette smoking or other known sources of bias.

Bhatia et al. (1998) found a small but consistent increase in the risk for lung cancer among workers with exposure to DE, in a quantitative meta-analysis of 23 studies that met criteria for inclusion. The observed RR estimates were greater than 1 in 21 of these studies. The pooled RR weighted by study precision was 1.33 (95% CI= 1.24, 1.44), which indicated increased RR for lung cancer from occupational exposure to diesel exhaust. Subanalyses by study design (case-control and cohort studies) and by control for smoking produced results that did not differ from those of the overall pooled analysis. Cohort studies using internal comparisons showed slightly higher RRs than those using external comparisons.

Lipsett and Campleman (1999) is a quantitative meta-analysis which identified 39 independent estimates of RR among 30 eligible studies of diesel exhaust and lung cancer published between 1975 and 1995. Pooled RRs for all studies and for study subsets were estimated using a random effects model. A pooled smoking-adjusted RR was 1.47 (95% CI = 1.29, 1.67). Substantial heterogeneity was found in the pooled-risk estimates. Adjustment for confounding by smoking, having a lower likelihood of selection bias, and increased study power were all found to contribute to lower heterogeneity and increased pooled estimates of RR.

The three aggregate analyses conclude that the data support a causal association between lung cancer and diesel exhaust exposure. Further, the analyses find that smoking is unlikely to account for the observed effects. On the other hand, Stöber and Abel (1996), Muscat and Wynder (1995), and Cox (1997) call into question the assertions by Cohen and Higgins (1995), Bhatia et al. (1998), and Lipsett and Campleman (1999) that the associations seen for diesel exhaust and lung cancer are unlikely to be due to bias. They argue that methodologic problems are prevalent among the studies, especially in evaluation of diesel engine exposure and control of confounding by cigarette smoking, and thus the observed associations are more likely to be due to bias. The conclusions of the two quantitative meta-analyses report on magnitude of pooled RR estimates and evaluation of potential sources of heterogeneity in the estimates. Despite the statistical sophistication of the meta-analyses,

the statistical models used cannot compensate for deficiencies in the original studies and will remain biased to the extent that bias exists in the original studies.

In view of the discussion of these studies, the body of epidemiologic evidence supports a causal association between exposure to DE and occurrence of lung cancer. The causality criteria of temporality, strength of association, consistency, and biological plausibility are generally satisfied. Temporality, that the exposure preceded the outcome, was established in all of the studies discussed above, including those in the meta-analyses. The strength of association was weak to modest (RRs/ORs between 1.2 and 2.6), with a dose-response relationship observed in several studies. Small increases in lung cancer relative risks (typically <2.0) potentially weaken the evidence of causality, because if confounders (e.g., smoking, asbestos exposure) were having an effect on the observed risk increases, then it could be enough to account for the increased risk. With the strongest risk factor for lung cancer being smoking, there is a lingering uncertainty as to whether smoking effects may be influencing the magnitude of the observed increased RRs, in spite of the fact that in key studies the investigating epidemiologists assert that they have effectively controlled for smoking. In studies in which the effects of smoking were controlled, increased RRs for lung cancer prevailed. While some studies did not have information on smoking, confounding by smoking is judged unlikely to be significant if the comparison populations were from the same socioeconomic class (see the Support Document for more information).

The lung cancer increase observed with diesel exhaust exposure in a number of studies is unlikely to be due to chance or bias. The excess risk is observed in both cohort and case-control designs, which contradicts the concern that a methodologic bias specifically characteristic of either design (e.g., recall bias) might account for the observed effect. Selection bias is certainly present in some of the occupational cohort studies that use external population data in estimating RRs, but this form of selection bias (a healthy worker effect) would only obscure, rather than spuriously produce, an association between DE and lung cancer. In effect, the usual standard mortality ratios observed in cohort mortality studies are likely to be underestimations of true risk. Selection biases may be operating in some case-control studies, but it is not obvious how such a bias could be sufficiently uniform in effect, prevalent, and strong enough to lead to the consistent association seen in the aggregate data. Given the variety of designs used in studying the DE and lung cancer association and the number of studies in different populations, it is unlikely that routinely studying noncomparable groups is an explanation for the consistent association seen.

Moreover, various methodologic limitations of individual studies have been considered, such as small sample size, short follow-up period, lack of data on confounding variables, use of death certificates to identify the lung cancer cases, and lack of latency analysis. The studies with small sample sizes (i.e., not enough power) and short follow-up periods (i.e., not enough latent period) have been difficult to interpret due to these limitations. Some other uncertainties are methodologic bias specifically characteristic of either cohort or case-control design, nondifferential misclassification of exposure and/or outcome bias (i.e. use of inaccurate surrogates for diesel exposure and lung cancer incidence can lead to substantial bias), and confounding by smoking. Finally, exposure information bias is certainly a problem for almost all of the studies concerned. For detailed discussion about these uncertainties see the Support Document (U.S. EPA, 2002; Section 7.2.4.4).

__II.A.3. Animal Carcinogenicity Data

Many animal studies have evaluated various aspects of the carcinogenic potential of whole diesel exhaust, including traditional chronic inhalation studies using rats, mice, hamsters, and

limited studies using cats and monkeys. Some of the studies used whole DE, while others used filtered DE (free of DPM) to differentiate gaseous phase effects from effects induced by the particle and its adsorbed organics. Other studies were designed to evaluate the relative importance of the carbon core of DPM versus that of the particle-adsorbed compounds, and a number of studies were carried out to determine the combined effects of inhaled DE and tumor initiators, promoters and cocarcinogens. The Support Document (U.S. EPA, 2002; Chapter 7.3) describes and discusses results from 27 studies.

It has been repeatedly shown that, with sufficient exposure, inhalation of DE is capable of inducing lung cancer in rats, several strains, males and females (Mauderly et al.,1987; Heinrich et al., 1986, 1995; Iwai et al., 1986, 1997; Ishinishi et al., 1988a; Takaki et al., 1989; Brightwell et al., 1986; Nikula et al., 1995). Although lung tumor responses correlate best with cumulative exposure (concentration x daily exposure duration x days of exposure), examination of rat data indicates a nonlinear trend, with increasing tumor incidence at exposures exceeding 1×10^4 mg hr/m³, and more generally with experimental chronic exposure concentrations at or greater than 3500 µg/m³. While tumorigenic responses were not observed at exposures less than those demonstrating particle overload exposure, thus supporting a hypothesis of a nonlinear response, the rat studies lack the sensitivity statistically to confirm the absence of response at lower doses. If low-dose effects do occur, it can be hypothesized that the organic constituents on the particle or in the gases, are playing a role. Notably, several reports (Wong et al., 1985; Bond et al., 1990) also make comment on a possible mode of action by providing evidence for DNA damage in rats. Exposures at or greater than 3500 µg/m³ are shown to result in lung particle overload, characterized by slowed particle clearance, lung tissue inflammation, lung pathology and eventually a tumorigenic response (ILSI, 2000). The rats develop adenomas, adenocarcinomas, and adenosquamous cell carcinomas, as well as squamous keratinizing lesions. This latter lesion appears for the most part to be unique to the rat, and may not have relevance for human safety evaluation (Boorman et al., 1996).

Studies in rats of particles (e.g., carbon black, titanium dioxide) such as those reported by Driscoll et al. (1996, 1997) support the existence of a nonlinear response if it is assumed that inflammation is a prerequisite for lung tumor induction. Evidence for the importance of DPM's carbon core was initially provided by studies of Kawabata et al. (1986), which showed induction of lung tumors in F344 rat following intratracheal instillation of carbon black that contained no more than traces of organics, and studies of Heinrich (1990) that indicated that exposure via inhalation to carbon black (Printex 90) particles induced rat lung tumors at concentrations similar to those effective in DPM studies. Additional studies by Heinrich et al. (1995) and Nikula et al. (1995) confirmed the capability of carbon particles to induce rat lung tumors. Rittinghausen et al. (1997) reported an increase in cystic keratinizing epitheliomas following intratracheal instillation of rats with either original DPM or DPM extracted to remove the organic fraction, with the unextracted particles inducing a slightly greater effect.

The evidence for a lung tumor response in other common strains of laboratory animals exposed to DE under standard inhalation protocols is equivocal. Inhalation of DE induced significant increases in lung tumors in female NMRI mice (Heinrich et al., 1986b; Stöber, 1986) and in female Sencar mice (Pepelko and Peirano, 1983). An apparent increase was also seen in female C57BL mice (Takemoto et al., 1986). However, in a repeat of their earlier study, Heinrich et al. (1995) failed to detect lung tumor induction in either NMRI or C57BL/6N mice. No increases in lung tumor rates were reported in a series of inhalation studies using strain A mice (e.g., Orthoefer et al., 1981). Mauderly et al. (1996) reported no tumorigenic responses in CD-1 mice exposed under conditions resulting in positive responses in rats. The successful induction of lung tumors in mice by Ichinose et al. (1997a,b) via

intratracheal instillation may have been the result of local deposition of larger doses. Positive effects in Sencar mice may be due to use of a strain sensitive to tumor induction in epidermal tissue by organic agents, as well as exposure from conception, although proof for such a hypothesis is lacking.

Attempts to induce significant increases in lung tumors in Syrian hamsters by inhalation of whole DE were unsuccessful (Heinrich et al., 1982, 1986b, 1989; Brightwell et al., 1986). Intratracheal instillation did not induce lung tumors in Syrian hamsters (Kunitake et al., 1986; Ishinishi et al., 1988b). However, hamsters are considered to be relatively insensitive to lung tumor induction (e.g., Dontenwill et al., 1973). Neither cats (Pepelko and Peirano, 1983) nor monkeys (Lewis et al., 1989) developed tumors following 2-year exposure to DE. These studies are less definitive, however, due to inadequate duration of these exposures for these longer-lived species, small group sizes, and exposure levels below the maximum tolerated dose (MTD).

Studies of filtered DE in laboratory animal species have been carried out to differentiate gaseous phase effects from effects induced by the particle and its adsorbed organics. Long-term exposure to DE filtered to remove particulate matter failed to induce lung tumors in rats (Heinrich et al., 1986a; Iwai et al., 1986; Brightwell et al., 1989), or in Syrian hamsters (Heinrich et al., 1986a; Brightwell et al., 1989). A significant increase in lung carcinomas was reported by Heinrich et al. (1986a) in NMRI mice exposed to filtered exhaust. However, in a more recent study the authors were unable to confirm earlier results in either NMRI or C57BL/6N mice (Heinrich et al., 1995). Although filtered exhaust appeared to potentiate the carcinogenic effects of DEN (Heinrich et al., 1982), because of the lack of positive data in rats and equivocal or negative data in mice it can be concluded that filtered exhaust is either not carcinogenic or has a low cancer potency.

Dermal exposure and subcutaneous (s.c.) and intraperitoneal (i.p.) injection in mice pro,0B8—023Fmx,3,CE

In summary, a number of intratracheal instillation studies in rats and mice exposed to high doses of whole diesel exhaust, and a variety of skin painting studies using extracts (organic fraction of whole diesel exhaust), provide animal evidence for carcinogenicity or the potential for carcinogenicity of DE or fractions of the DE mixture, in addition to the many chronic inhalation rats studies showing a positive lung cancer at high exposures. The rat evidence, however, is not relevant for human hazard characterization that is focused on environmental levels of exposure, where a human lung particle overload is not expected (note that a preliminary 75^{th} percentile nationwide estimate of DE human environmental exposure for 1996 is about 1.7 $\mu g/m^3$). The contribution of the various fractions of DE to the carcinogenic response is uncertain beyond that which can been seen in rats. Inhalation exposure to filtered exhaust generally failed to induce lung tumors in animal species. The presence of known carcinogens and mutagens adsorbed to diesel particles and the demonstrated tumorigenicity of particle extracts in a variety of injection, instillation, and skin-painting studies indicates a carcinogenic potential for the organic fraction.

__II.A.4. Supporting Data for Carcinogenicity

For the human, it is not clear what constituent(s) of DPM or the whole diesel exhaust could be responsible for the observed lung cancer. DNA adduct formation and/or mutations in blood cells following exposure to DE, especially at levels insufficient to induce lung overload, can be presumed to be the result of organics diffusing into the blood. Hemminki et al. (1994) reported increased levels of DNA adducts in lymphocytes of bus maintenance and truck terminal workers. Österholm et al. (1995) studied mutations at the hprt-locus of T-lymphocytes in bus maintenance workers. Although they were unable to identify clear-cut exposure-related differences in types of mutations, adduct formation was significantly increased in the exposed workers. Nielsen et al. (1996) reported significantly increased levels of lymphocyte DNA adducts, hydroxyvaline adducts in hemoglobin, and 1-hydroxypyrene in urine of garage workers exposed to DE.

An extensive array of studies with DPM and gaseous fractions of diesel exhaust has demonstrated mutagenic activity in *Salmonella* and several vitro mammalian cell lines, and structural chromosome aberrations and increased sister chromatid exchanges (SCE) in mammalian cells. On the other hand, dilutions of whole diesel exhaust did not induce sex-linked recessive lethals in *Drosophila* or specific-locus mutations in male mouse germ cells. Whole exhaust induced micronuclei but not SCE or structural aberrations in bone marrow of male Chinese hamsters exposed to whole diesel engine exhaust for 6 mo. In a shorter exposure (7 weeks), neither micronuclei nor structural aberrations were increased in bone marrow of female Swiss mice. Likewise, whole diesel exhaust did not induce dominant lethals or heritable translocations in male mice exposed for 7.5 and 4.5 weeks, respectively. All of these studies are discussed in the Support Document (U.S. EPA, 2002).

The application of mutagenicity data to the question of the potential carcinogenicity of diesel engine exhaust is based on the premise that genetic alterations are found in all cancers and that several of the chemicals found in diesel engine exhaust possess mutagenic activity in a variety of genetic assays. These genetic alterations can be produced by gene mutations, deletions, translocations, aneuploidy, or amplification of genes, hence no single genotoxicity assay should be expected to either qualitatively or quantitatively predict rodent carcinogenicity. With diesel engine exhaust or other mixtures, additional complications arise because of the complexity of the material being tested.

In addition to the toxicological evidence associating lung tumors with DPM, many of the other constituents of DE are known to have mutagenic and carcinogenic properties. California EPA

(Cal EPA, 1998) identified at least 19 hydrocarbons present in DE that are known or suspected carcinogens, according to evaluations by the International Agency for Research on Cancer (IARC, 1989). The organic compounds present in the DE gases and adsorbed onto the particles include a wide spectrum of compounds which originate from unburned diesel fuel, lube oil, low levels of partial combustion, and pyrolysis products, including: alkanes, alkenes, aldehydes, monocyclic aromatic compounds, and polycyclic aromatic hydrocarbons (PAHs). The principal aldehydes are formaldehyde, acetaldehyde and acrolein. Other gaseous components of DE include benzene, 1,3-butadiene, and nitro-PAHs (including those with ≤4 rings and nitro-PAHs with 2 and 3 rings). PAHs and their derivatives comprise <1% of the DPM mass. See the Support Document (U.S. EPA, 2002) for more details.

__II.A.5. Additional Comments

Several organizations have reviewed available relevant data and evaluated the potential human carcinogenicity of DE or DPM, and have concluded that DE is probably carcinogenic to humans (IARC, 1989; IPCS, 1996), or is reasonably anticipated to be a carcinogen (NTP, 2000).

The relevance of this hazard characterization to current ambient DE exposures hinges on recognizing that the health effects data are derived from engine technologies and fuels that existed in the past, and that some changes in the DE exhaust mixture have occurred and can be expected in the future (see the Support Document (U.S. EPA, 2002), Section 2). Although decreases in amount and changes in composition of DE engine exhaust have occurred over time for on-road engines, a change is slow to manifest in the environment because vehicular fleet turnover is slow. Available studies have not focused on the potential toxicological effect of the emission changes. There is no compelling evidence at present to show that past and present exhaust characteristics are so toxicologically dissimilar as to render the current use of the assessment's findings outdated. It is clear that with the implementation of U.S. EPA's regulations affecting 2007 model year on-road diesel engines, the exhaust from these engines will be notably different and thus the hazard potential for this exhaust would need to be re-evaluated.

__II.A.6. Discussion of Confidence

While the weight-of-evidence indicates that DE has the potential to pose a lung cancer hazard to humans at anticipated levels of environmental exposure, as shown by occupational epidemiology studies, a confident dose-response relationship based on occupational exposure levels is currently lacking. Among the occupational studies, the railroad worker studies (Garshick et al., 1987, 1988) and the Teamsters Union truck driver studies (Steenland et al., 1990) are considered to have the best available combination of response and surrogate exposure information (based on worker years in a job category) for possible use in establishing exposure-response relationships and thereafter deriving a cancer unit risk. There have been different views on the suitability of the railroad workers and Teamster Union truck drivers set of studies for estimating environmental cancer risks (e.g., Cal EPA, 1998; Cohen and Higgins, 1995; HEI, 1999). Given the equivocal evidence for the presence or absence of an exposure-response relationship for the studies of railroad workers, and current exposure uncertainties for the study of truck drivers, it is judged that available data are too uncertain at this time for a confident quantitative dose-response analysis and subsequent derivation of cancer unit risk for DE.

Even though occupational data are considered most relevant for use in dose-response assessment, the following data gaps and uncertainties must be critically evaluated before a confident dose-response can be recommended:

the lack of actual DE exposure data for workers in the available epidemiologic studies;
the lack of DE exposure data for controls in the available epidemiologic studies, owing to the presence of diesel engine exhaust in ambient air for non-occupational settings;
possible confounders (smoking and asbestos exposure) that could contribute to the observed lung cancer risk in occupational studies of DE if the control for these confounders is not adequate;
whether or not an exposure-response relationship for occupational lung cancer risk can be estimated for DE:
the use of DPM (expressed as μg/m³) as a surrogate dosimeter for DE exposure, given that the relative roles of various constituents in mediating carcinogenic effects and the carcinogenic mode of action are still not known, and
the representativeness of occupational populations for the general population and vulnerable subgroups, including infants and children and individuals with preexisting diseases, particularly respiratory conditions.

Use of animal data to develop dose-response based unit cancer risk values was judged inappropriate, since the only animal model with direct inhalation exposure and lung tumor responses was the rat, and the rat results were discounted because of mode-of-action information showing that the high exposure rat responses would not be a suitable basis for human dose-response analysis at environmental levels of exposure.

_II.B. Quantitative Estimate of Carcinogenic Risk from Oral Exposure

N.A. There are no chronic data from which to estimate carcinogenic risk from oral exposure. All available studies are focused on inhalation exposure.

_II.C. Quantitative Estimate of Carcinogenic Risk from Inhalation Exposure

N.A. The absence of adequate data to develop a sufficiently confident dose-response relationship from the epidemiologic studies has prevented the estimation of inhalation carcinogenic risk.

_II.D. EPA Documentation, Review, and Contacts (Carcinogenicity Assessment)

__II.D.1. EPA Documentation

Source Document — U.S. EPA, 2002

The Health Assessment Document (HAD) (U.S. EPA, 2002) on which this IRIS Summary is based was peer reviewed by EPA's Clean Air Science Advisory Committee (CASAC) in October 2000. Written comments from CASAC were received in December 2000. Their comments were evaluated carefully and incorporated in finalization of the HAD. A record of these comments is available with the HAD.

__II.D.2. EPA Review (Carcinogenicity Assessment)

Agency Consensus Date -1/31/03

__II.D.3. EPA Contacts (Carcinogenicity Assessment)

Please contact the IRIS Hotline for all questions concerning this assessment or IRIS, in general, at (202)566-1676 (phone), (202)566-1749 (FAX) or hotline.iris@epa.gov (email address).

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_VI. Bibliography

Last Revised — 02/28/2003

_VI.A. Oral RfD References

N.A.

_VI.B. Inhalation RfC References

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_VII. Revision History

Substance Name — Diesel engine exhaust
CASRN — N.A.

Date	Section	Description
07/01/1992	I.B.	Inhalation RfC now under review
08/01/1992	I.B.6.	Work group review date added
06/01/1993	I.B.	Inhalation RfC on-line
06/01/1993	VI.B.	Inhalation RfC references on-line
07/01/1993	VI.B.	Minor corrections made
04/01/1997	III., IV., V.	Drinking Water Health Advisories, EPA Regulatory Actions, and Supplementary Data were removed from IRIS on or before April 1997. IRIS users were directed to the appropriate EPA Program Offices for this information.
02/28/2003	I.B., II.	RfC, Cancer sections updated based on new health assessment document.

_VIII. Synonyms

Substance Name — Diesel engine exhaust
CASRN — N.A.
Last Revised — 02/28/2003

diesel soot
diesel particulate matter
dpm

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